

**Amendments to the Specification:**

Please replace paragraph [01] with the following amended paragraph:

[01] ~~This application is a continuation in part patent application of the following pending U.S. patent applications:~~

<u>Title</u>	<u>No.</u>	<u>Serial</u>	<u>Filing Date</u>
Human Esterase D, Its Uses and a Process of Purification		091,547	August 31, 1987
ppRB <sup>110</sup> nuclear phosphoprotein The Retinoblastoma Susceptibility Gene Product		098,612	September 17, 1987
Retinoblastoma Gene Cancer Suppressing and Regulator		108,748	October 15, 1987

This application is a continuation of pending application USSN 08/472,760, filed June 5, 1995, which is a continuation in part of USSN 08/276,041 (abandoned), filed July 14, 1994, which is a continuation of USSN 07/764,714 (abandoned), filed September 24, 1991, which is a continuation of USSN 07/265,829 (abandoned), filed October 31, 1988.

Please replace paragraph [19] with the following amended paragraph:

[19] Additionally, ~~pending~~ U.S. patent application, Serial No. 098,612 (now U.S. Patent No. 4,942,123 Jul. 17, 1990), discloses a phosphoprotein ppRB<sup>110</sup> which is primarily located in the cell nucleus and has DNA binding activity. As with RB mRNA, this protein was detected in many types of cultured human cells. pp110<sup>RB</sup> has been shown to form a tight association with large T antigen and E1A, the transforming proteins of DNA tumor viruses SV40 and adenovirus respectively, *Nature*, 334:124 (1988); *Cell*, 54:275 (1988). The RB gene product, or a complex containing it, has been found to have DNA binding activity, *Nature*, 329:642 (1987). These studies indirectly suggested that pp110<sup>RB</sup> has a role in regulating the expression of other cellular genes, and may also mediate the oncogenic effects of some viral transforming proteins.

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Please replace paragraph [21] with the following amended paragraph:

[21] In this regard, in ~~pending~~ U.S. application, Serial No. 091,547 (now U.S. Patent. No. 5,011,773), there is described methods for using cloned human esterase D cDNA as a genetic marker as a diagnostic tool for retinoblastoma, Wilson's disease, and other hereditary or acquired diseases controlled by genes located at the 13 chromosome 13q:1411 region. The patent application discloses an esterase D cDNA probe for cloning the retinoblastoma gene, and the use of the cloned human esterase cDNA as a prognostic tool for determination of genetic predisposition to retinoblastoma or Wilson's disease.

Please replace paragraph [41] with the following amended paragraph:

[41] ~~FIG. 3 shows cultures of RB and Lux virus infected tumor cells after G418 selection;~~  
FIG. 3A to FIG. 3F depict morphological effects of Rb or Lux virus infection in retinoblastoma and osteosarcoma cell lines. WERI-Rb27 (FIG. 3A and 3D), Saos-2 ( FIG. 3B and 3E), and U20S (FIG. 3C and 3F) cells were infected with Lux virus (FIG. 3A-3C) or Rb virus (FIG. 3D-3F) and cultured in G418-containing media for 8 weeks (WERI-Rb27) for 4 weeks (Saos-2 and U-20S);

Please replace paragraph [42] with the following amended paragraph:

[42] ~~FIG. 4A through Fig. 4C shows show~~ graphs of WERI-Rb27 (FIG. 4A), Saos-2 (FIG. 4B) and U-20S (FIG. 4C) ~~each cell~~ colony growth over a five day period; and

Please replace paragraph [77] with the following amended paragraph:

[77] While the following summarizes the utilization of human esterase D cDNA as a genetic marker, for a complete disclosure of the method, reference may be made to ~~pending~~ patent application, Ser. No. 091,547 (now U.S. Patent. No. 5,011,773).

Please replace paragraph [85] with the following amended paragraph:

[85] In the ~~pending~~ U.S. patent application Serial No. 091,547 (now U.S. Patent. No. 5,011,773), a process was disclosed for purifying human ESD by first obtaining the human ESD from human tissue, lysing said tissue, extracting the lysed tissue with an organic solvent, partially purifying the extract and then separating the purified ESD by column chromatography.

Please replace paragraph [116] with the following amended paragraph:

[116] After identification of the RB gene its cDNA sequence and genomic organization were determined. Pending U.S. patent application Serial No. 098,612 (now U.S. Patent. No. 4,942,123 Jul. 17, 1990) discloses the amino acid sequence of a phosphoprotein located in the cell nucleus and having DNA binding activity.

Please replace paragraph [126] with the following amended paragraph:

[126] Through the method disclosed in ~~pending~~ patent application Serial No. 108,748, filed Oct. 15, 1987, now abandoned, a gene encoding a messenger RNA (mRNA) of 4.6 kilobases (kb), located in the proximity of esterase D, was identified as the retinoblastoma susceptibility gene on the basis of chromosomal location, homozygous deletion, and tumor-specific alterations in expression. Transcription of this gene was abnormal in six of six retinoblastomas examined. In contrast, full-length RB mRNA was present, in human fetal retina and placenta tumors, and in other tumors such as neuroblastoma and medulloblastoma. DNA from retinoblastoma cells had a homozygous gene deletion in one case and hemizygous deletion in another case, while the remainder were not grossly different from normal human control DNA.

Please replace paragraph [161] with the following amended paragraph:

[161] As a specific example of the technique herein disclosed, the protein product of the RB gene has been identified.. According to the method disclosed in ~~pending~~ U.S. patent application Serial No. 098,612 (now U.S. Patent. No. 4,942,123 Jul. 17, 1990), immunoprecipitation of the phosphoprotein was accomplished utilizing preimmune rabbit anti-sera and, as disclosed in said application, a protein with MW 110-114kD was immunoprecipitated with anti-ppRB<sup>110</sup> IgG.

Please replace paragraph [164] with the following amended paragraph:

[164] While the identification of ppRB<sup>110</sup> is summarized herein, for a complete disclosure thereof, reference may be made to the foregoing identified ~~pending~~ patent application Serial No. 098,612 (now U.S. Patent. No. 4,942,123 Jul. 17, 1990).

Please replace paragraph [165] with the following amended paragraph:

[165] As stated in ~~pending~~ U.S. patent application, Serial No 098,612 (now U.S. Patent. No. 4,942,123 Jul. 17, 1990), experimental evidence indicates that complete inactivation of the RB gene is required for tumor formation, and that a new mode of function exists for the RB gene as a suppressing of the cancer phenotype.

Please replace paragraph [225], lines 1 and 2 on page 44 with the following amended lines:

[225] ~~Pending~~ U.S. patent application Serial No. 108,748 filed Oct. 15, 1987, now abandoned, discloses and claims the RB gene and its clone. The RB gene and its clone had the nucleotide sequence depicted in Table 2.